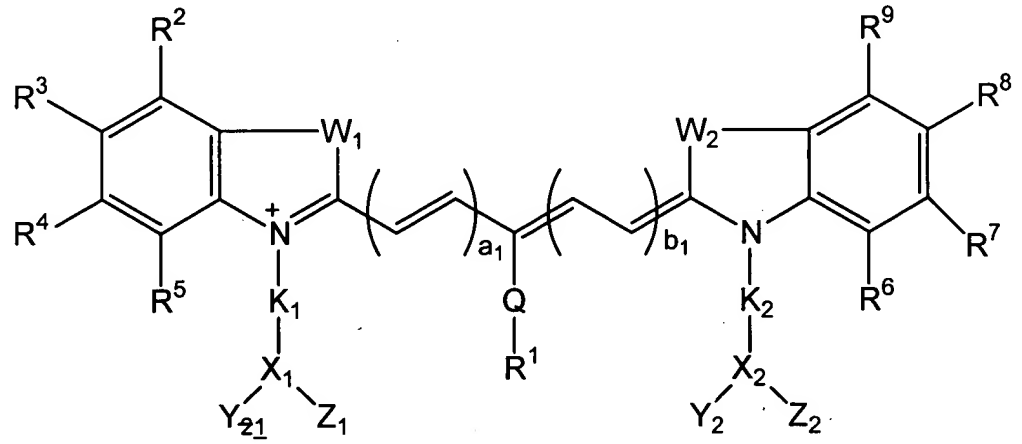
IN THE SPECIFICATION

Replace the paragraph beginning on page 5, line 22, and ending on page 8, line 7, with the following rewritten paragraph:

The invention relates to novel compositions comprising cyanine dyes having a general formula 1



Formula 1

wherein W_1 and W_2 may be the same or different and are selected from the group consisting of $-CR^{10}R^{11}$, -O-, $-NR^{12}$, -S-, and –Se; Y_1, Y_2, Z_1, and Z_2 are independently selected from the group consisting of hydrogen, tumor-specific agents, phototherapy

agents, -CONH-Bm, -NHCO-Bm, -$(CH_2)_a$-CONH-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-CONH-Bm, -$(CH_2)_a$-NHCO-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-NHCO-Bm, -$(CH_2)_a$-N(R^{12})-$(CH_2)_b$-CONH-Bm, -$(CH_2)_a$-N(R^{12})-$(CH_2)_c$-NHCO-Bm, -$(CH_2)_a$-N(R^{12})-CH_2-$(CH_2OCH_2)_b$-CH_2-CONH-Bm, -$(CH_2)_a$-N(R^{12})-CH_2-$(CH_2OCH_2)_b$-CH_2-NHCO-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-$(CH_2)_a$-CONH-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-$(CH_2)_a$-NHCO-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-CH_2-$(CH_2OCH_2)_d$-CONH-Bm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-CH_2-$(CH_2OCH_2)_d$-NHCO-Bm, -CONH-Dm, -NHCO-Dm, -$(CH_2)_a$-CONH-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-CONH-Dm, -$(CH_2)_a$-NHCO-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-NHCO-Dm, -$(CH_2)_a$-N(R^{12})-$(CH_2)_b$-CONH-Dm, -$(CH_2)_a$-N(R^{12})-$(CH_2)_c$-NHCO-Dm, -$(CH_2)_a$-N(R^{12})-CH_2-$(CH_2OCH_2)_b$-CH_2-CONH-Dm, -$(CH_2)_a$-N(R^{12})-CH_2-$(CH_2OCH_2)_b$-CH_2-NHCO-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-$(CH_2)_a$-CONH-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-$(CH_2)_a$-NHCO-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-CH_2-$(CH_2OCH_2)_d$-CONH-Dm, -CH_2-$(CH_2OCH_2)_b$-CH_2-N(R^{12})-CH_2-$(CH_2OCH_2)_d$-NHCO-Dm, -$(CH_2)_a$-N $R^{12}R^{13}$, and -$CH_2(CH_2OCH_2)_b$-CH_2N $R^{12}R^{13}$; K_1 and K_2 are independently selected from the group consisting of C_1-C_{30} alkyl, C_5-C_{30} aryl, C_1-C_{30} alkoxyl, C_1-C_{30} polyalkoxyalkyl, C_1-C_{30} polyhydroxyalkyl, C_5-C_{30} polyhydroxyaryl, C_1-C_{30} aminoalkyl, saccharides, peptides, -$CH_2(CH_2OCH_2)_b$-CH_2-, -$(CH_2)_a$-CO-, -$(CH_2)_a$-CONH-, -CH_2-$(CH_2OCH_2)_b$-CH_2-CONH-, -$(CH_2)_a$-NHCO-, -CH_2-$(CH_2OCH_2)_b$-CH_2-NHCO-, -$(CH_2)_a$-O-, and -CH_2-$(CH_2OCH_2)_b$-CO-; X_1 and X_2 are single bonds, or are independently selected from the group consisting of nitrogen, saccharides, -CR^{14}-, -$CR^{14}R^{15}$, -$NR^{16}R^{17}$; $C_5 - C_{30}$ aryl; Q is a single bond or is selected from the group consisting of -O-, -S-, -Se-, and –NR^{18}; a_1 and b_1 independently vary from 0 to 5; R^1 to R^{13}, and R^{18} are independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_5-C_{20} aryl, C_1-C_{10} alkoxyl, C_1-C_{10} polyalkoxyalkyl, C_1-C_{20} polyhydroxyalkyl, C_5-C_{20}

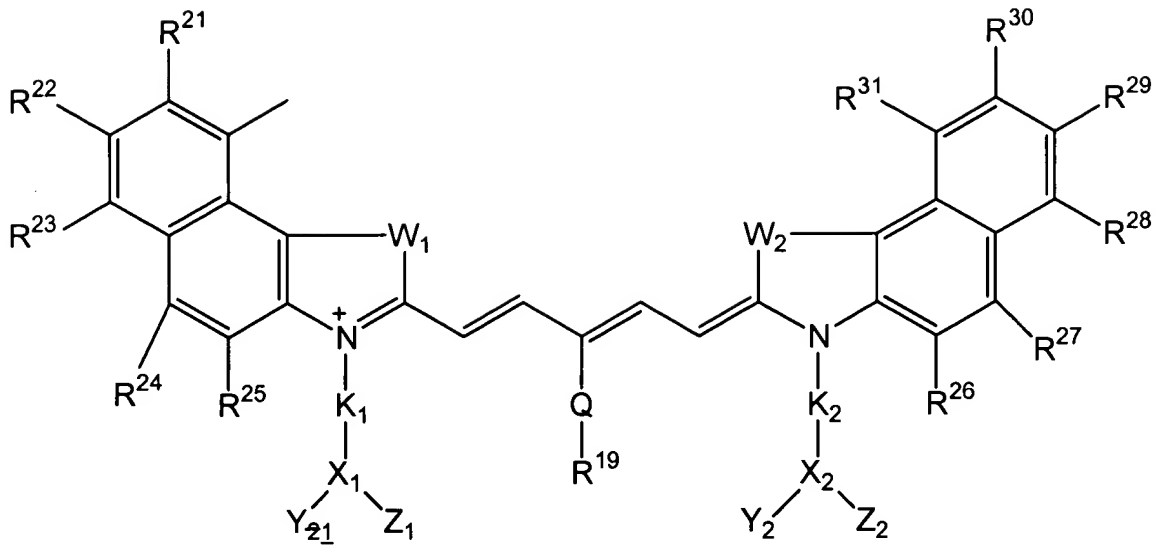
polyhydroxyaryl, C_1-C_{10} aminoalkyl, cyano, nitro, halogens, saccharides, peptides, $-CH_2(CH_2OCH_2)_b-CH_2-OH$, $-(CH_2)_a-CO_2H$, $-(CH_2)_a-CONH-Bm$, $-CH_2-(CH_2OCH_2)_b-CH_2-CONH-Bm$, $-(CH_2)_a-NHCO-Bm$, $-CH_2-(CH_2OCH_2)_b-CH_2-NHCO-Bm$, $-(CH_2)_a-OH$ and $-CH_2-(CH_2OCH_2)_b-CO_2H$; R^{14} to R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_5-C_{20} aryl, C_1-C_{10} alkoxyl, C_1-C_{10} polyalkoxyalkyl, C_1-C_{20} polyhydroxyalkyl, C_5-C_{20} polyhydroxyaryl, C_1-C_{10} aminoalkyl, saccharides, peptides, $-CH_2(CH_2OCH_2)_b-CH_2-$, $-(CH_2)_a-CO-$, $-(CH_2)_a-CONH-$, $-CH_2-(CH_2OCH_2)_b-CH_2-CONH-$, $-(CH_2)_a-NHCO-$, $-CH_2-(CH_2OCH_2)_b-CH_2-NHCO-$, $-(CH_2)_a-O-$, and $-CH_2-(CH_2OCH_2)_b-CO-$; Bm and Dm are independently selected from the group consisting of bioactive peptides, proteins, cells, antibodies, antibody fragments, saccharides, glycopeptides, peptidomimetics, drugs, drug mimics, hormones, metal chelating agents, radioactive or nonradioactive metal complexes, echogenic agents, photoactive molecules, and phototherapy agents (photosensitizers); a and c independently vary from 1 to 20; b and d independently vary from 1 to 100.

A1

Replace the paragraph beginning on page 8, line 8, and ending on page 9, line 3, with the following rewritten paragraph:

The invention also relates to the novel composition comprising carbocyanine dyes having a general formula 2

A2

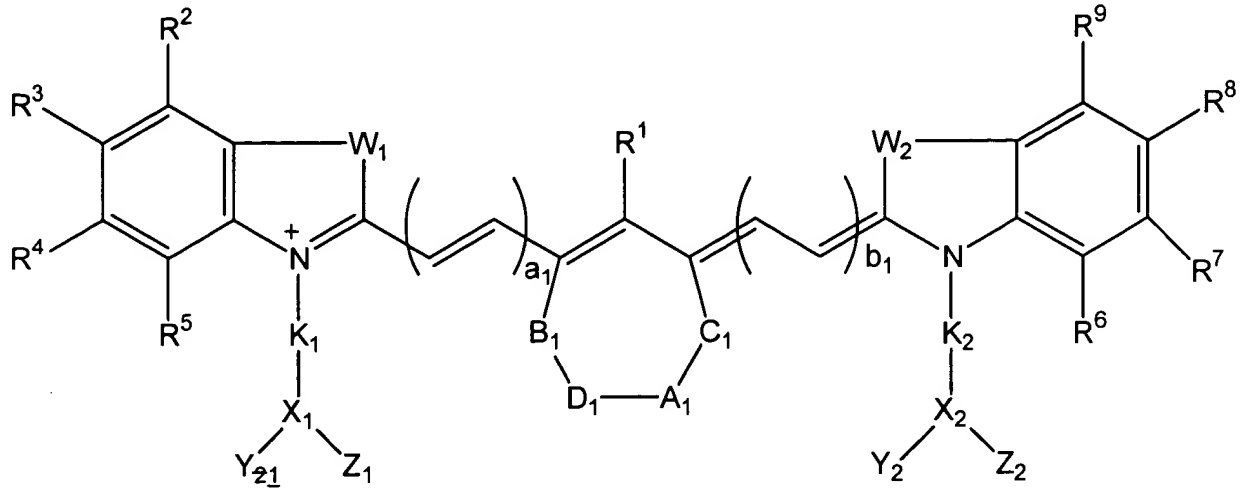


Formula 2

wherein W_1, W_2, Y_1, Y_2, Z_1, Z_2, K_1, K_2, Q, X_1, X_2, a_1, and b_1 are defined in the same manner as in Formula 1; and R^{19} to R^{31} are defined in the same manner as R^1 to R^9 in Formula 1.

Replace the paragraph beginning on page 9, line 4, and ending on page 10, line 2, with the following rewritten paragraph:

The invention also relates to the novel composition comprising carbocyanine dyes having a general formula 3

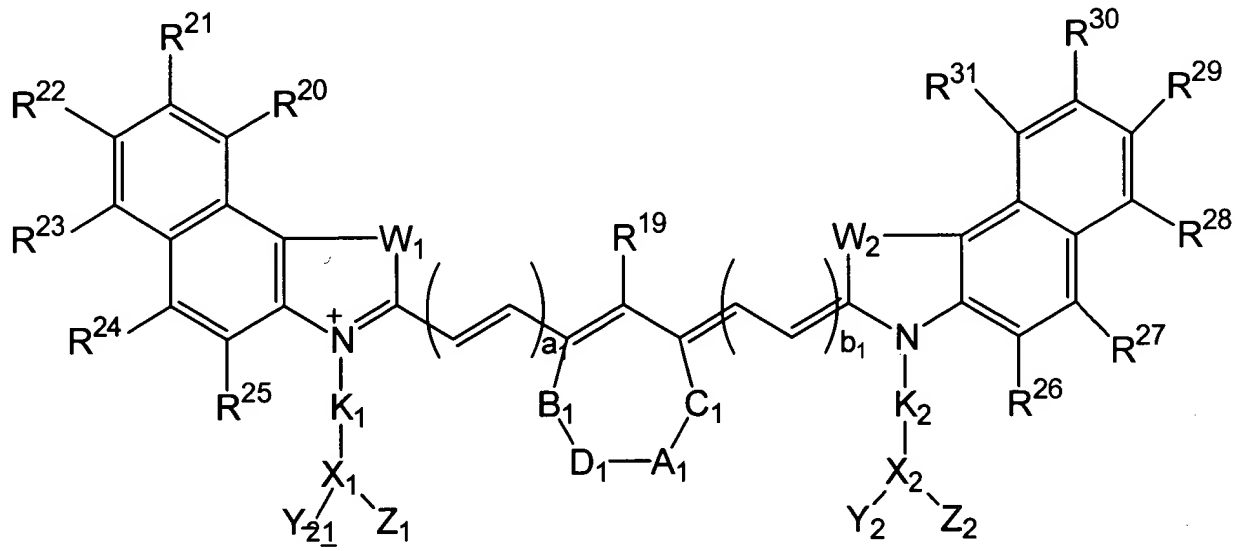


Formula 3

wherein A_1 is a single or a double bond; B_1, C_1, and D_1 are independently selected from the group consisting of -O-, -S-, -Se-, -P-, $-CR^{10}R^{11}$, $-CR^{11}$, alkyl, NR^{12}, and -C=O; A_1, B_1, C_1, and D_1 may together form a 6- to 12-membered carbocyclic ring or a 6- to 12-membered heterocyclic ring optionally containing one or more oxygen, nitrogen, or sulfur atoms; and W_1, W_2, Y_1, Y_2, Z_1, Z_2, K_1, K_2, X_1, X_2, a_1, b_1, and R^1 to R^{12} are defined in the same manner as in Formula 1.

Replace the paragraph beginning on page 10, line 3, and ending on page 10, line 10, with the following rewritten paragraph:

The present invention also relates to the novel composition comprising carbocyanine dyes having a general formula 4



Formula 4

wherein A_1, B_1, C_1, and D_1 are defined in the same manner as in Formula 3; W_1, W_2, Y_1, Y_2, Z_1, Z_2, K_1, K_2, X_1, X_2, a_1, and b_1 are defined in the same manner as in Formula 1; and R^{19} to R^{31} are defined in the same manner as R^1 to R^9 in Formula 1.

R place th paragraph beginning on pag 13, line 7, and ending on page 14, line 9, with the following rewritten paragraph:

In two other ~~embodiment~~ embodiments, the bioconjugates according to the present invention have the formulas 3 or 4 wherein W_1 and W_2 may be the same or different and are selected from the group consisting of $-C(CH_3)_2$, $-C((CH_2)_aOH)CH_3$, $-C((CH_2)_aOH)_2$, $-C((CH_2)_aCO_2H)CH_3$, $-C((CH_2)_aCO_2H)_2$, $-C((CH_2)_aNH_2)CH_3$, $-C((CH_2)_aNH_2)_2$, $-C((CH_2)_aNR^{12}R^{13})_2$, $-NR^{12}$, and -S-; Y_1 and Y_2 are selected from the group consisting of hydrogen, tumor-specific agents, -CONH-Bm, -NHCO-Bm, $-(CH_2)_a$-CONH-Bm, $-CH_2-(CH_2OCH_2)_b-CH_2$-CONH-Bm, $-(CH_2)_a$-NHCO-Bm, $-CH_2-(CH_2OCH_2)_b-CH_2$-NHCO-Bm, $-(CH_2)_a-NR^{12}R^{13}$, and $-CH_2(CH_2OCH_2)_b-CH_2NR^{12}R^{13}$; Z_1 and Z_2 are independently selected from the group consisting of hydrogen, phototherapy agents, -CONH-Dm, -NHCO-Dm, $-(CH_2)_a$-CONH-Dm, $-CH_2-(CH_2OCH_2)_b-CH_2$-CONH-Dm, $-(CH_2)_a$-NHCO-Dm, $-CH_2-(CH_2OCH_2)_b-CH_2$-NHCO-Dm, $-(CH_2)_a-N\ R^{12}R^{13}$, and $-CH_2(CH_2OCH_2)_b-CH_2N\ R^{12}R^{13}$; K_1 and K_2 are independently selected from the group consisting of C_1-C_{10} alkyl, C_5-C_{20} aryl, C_1-C_{20} alkoxyl, C_1-C_{20} aminoalkyl, $-(CH_2)_a$-CO-, $-(CH_2)_a$-CONH, $-CH_2-(CH_2OCH_2)_b-CH_2$-CONH-, $-(CH_2)_a$-NHCO-, $-CH_2-(CH_2OCH_2)_b-CH_2$-NHCO-, and $-CH_2-(CH_2OCH_2)_b$-CO-; X_1 and X_2 are single bonds or are independently selected from the group consisting of nitrogen, $-CR^{14}$-, $-CR^{14}R^{15}$, and $-NR^{16}R^{17}$; A_1 is a single or a double bond; B_1, C_1, and D_1 are independently selected from the group consisting of -O-, -S, $-CR^{11}$, alkyl, NR^{12}, and -C=O; A_1, B_1, C_1, and D_1 may together form a 6- to 12-membered carbocyclic ring or a 6- to 12-membered heterocyclic ring

optionally containing one or more oxygen, nitrogen, or sulfur atoms; a_1 and b_1 independently vary from 0 to 3; Bm is selected from the group consisting of bioactive peptides containing 2 to 30 amino acid units, proteins, antibody fragments, mono- and oligosaccharides; bioactive peptides, protein, and oligosaccharide; Dm is selected from the group consisting of photosensitizers, photoactive molecules, and phototherapy agents; a and c independently vary from 1 to 20; and b and d independently vary from 1 to 100.

Replace the heading on page 20, lines 20 to 21 with the following rewritten heading:

Synthesis of Peptide-Dye Conjugates (Figure 1B, n=4 R_1 = octreotate, R_2 = R_1 or ~~OH?~~ OH)

Replace the paragraph beginning on page 20, line 22, and ending on page 21, line 13, with the following rewritten paragraph:

Octreotate-bispentylcarboxymethylindocyanine dye was prepared as described in Example 4 with some modifications. Bispentylcarboxymethylindocyanine dye (60 mg, 75 µmoles) was added to 400 ~~ul~~ µl activation reagent consisting of 0.2 M HBTU/HOBt and 0.2 M ~~of~~ diisopropylethylamine in DMSO. The activation was complete in about 30 minutes and the resin-bound peptide (25 µmoles) was added to the dye. The reaction was carried out at ambient temperature for 3 hours. The mixture was filtered and the solid residue was washed with DMF, acetonitrile and THF. After drying the green residue, the peptide was cleaved from the resin and the side chain

protecting groups were removed with a mixture of trifluoroacetic acid:water:thioanisole:phenol (85:5:5:5$^{v/v}$). The resin was filtered and cold t-butyl methyl ether (MTBE) was used to precipitate the dye-peptide conjugate. The conjugate was dissolved in acetonitrile:water (2:3$^{v/v}$) and lyophilized. The product was purified by HPLC to give octreotate-1,1,2-trimethyl-[1H]-benz[e]indole propanoic acid conjugate (~~10%,~~ 10%), monooctreotate-bispentylcarboxymethylindocyanine dye (Cytate 3, 60%, n = 4, R_2 = OH) and bisoctreotate-bispentylcarboxymethylindocyanine dye (Cytate 4, 30%, n = 4, $R_1 = R_2$).

Replace the paragraph beginning on page 21, line 17, and ending on page 22, line 8, with the following rewritten paragraph:

Bispentylcarboxymethylindocyanine dye (cyhex, 60 mg, 75 µmoles) in dichloromethane is reacted with cyanuric acid fluoride (21 mg, 150 mmoles) in the presence of pyridine (12 mg, 150 mmoles) for 30 minutes to produce an acid anhydride. One molar equivalent of 2-[1-hexyloxyethyl]-2-devinylpyropheophorbide-a (HPPH, Figure 1D, T = -$NHC_2H_4NH_2$) is added to the anhydride to form the cyhex-HPPH conjugate with a free carboxylic acid group. This intermediate is added to an activation reagent consisting of a 0.2 M solution of HBTU/HOBt in DMSO (400 µl), and a 0.2 M solution of diisopropylethylamine in DMSO (400 µl). Activation of the carboxylic acid is complete in about 30 minutes. Resin-bound peptide (octreotate, 25 µmoles), ~~is~~ prepared as described in Example 4, is added to the mixture. The reaction is carried out at ambient temperature for 8 hours. The mixture is filtered ~~at~~ and the solid residue

is washed with DMF, acetonitrile and THF. After drying the dark residue at ambient temperature, the peptide derivative is cleaved from the resin and the side chain protecting groups are removed with a mixture of trifluoroacetic acid:water:thioanisole:phenol (85:5:5:5$^{v/v}$). After filtering the resin, cold t-butyl methyl ether (MTBE) is used to precipitate the dye-peptide conjugate, which is then lyophilized in acetonitrile:water (2:3$^{v/v}$).

Replace the paragraph on page 22, lines 22 to 26, with the following rewritten paragraph:

Orthogonally protected Fmoc-lysine(Mtt)^0 Octreotate was prepared on a solid support, as described in Examples 3 and 4. The Fmoc group of Fmoc-lysine(Mtt)^0 is removed from the solid support with 20% piperidine in DMF. HPPH (Figure 1D, T = -OH), pre-activated with HBTU coupled to the free ~~a-amino~~ ∝-amino group of lysine.

Replace the paragraph beginning on page 28, line 22, and ending on page 29, line 12 with the following rewritten paragraph:

The method for photodynamic therapy is well documented in the literature [Rezzoug H., et al. In Vivo Photodynamic Therapy with meso-Tetra (m-hydroxyphenyl)chlorin (mTHPC): Influence of Light Intensity and Optimization of Photodynamic Efficiency. *Proc.* SPIE (1996), 2924, 181-186; Stranadko E., et al. Photodynamic Therapy of Recurrent Cancer of Oral Cavity, an Alternative to Conventional Treatment. *Proc.* SPIE (1996), 2924, 292-297]. A solution of the peptide-

dye-phototherapy bioconjugate is prepared as described in Example 7 (5 µmol/mL of 15% DMSO in water, 0.5 mL) and is injected into the tail vein of the tumor-bearing rat. The rat is imaged 24 hours post injection as described in Examples 9-11 to localize the tumor. Once the tumor region is localized, the tumor is irradiated with light of 700 nm (which corresponds to the maximum absorption wavelength of HPPH, the component of the conjugate that effects PDT). The energy of radiation is 10 J/cm^2 at 160 mW/cm^2. The laser light is ~~transmtited~~ transmitted through a fiber optic, which is directed to the tumor. The rat is observed for 7 days and any decrease in tumor volume is noted. If the tumor is still present, a second dose of irradiation is repeated as ~~descried~~ described above until the tumor is no longer palpable.

Replace the paragraph on page 29, lines 13 to 18, with the following rewritten paragraph:

For localized therapy, a diagnostic amount of cytate (0.5 mL/0.2 ~~Kg~~ kg rat) is injected into the tail vein of the tumor-bearing rat and optical images are obtained as described in Examples 9-11. A solution of the peptide-dye-phototherapy bioconjugate is prepared as described in Example 7 (5 µmol/mL of 15% DMSO in water, 1.5 mL) and is injected directly into the tumor. The tumor is irradiated as described above.